Complete Summary

GUIDELINE TITLE

Interferon-alfa in the treatment of patients with inoperable locally advanced metastatic renal cell cancer: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Canil C, Hotte S, Mayhew LA, Waldron T, Winquist E, Genitourinary Cancer Disease Site Group. Interferon-alfa in the treatment of patients with inoperable locally advanced or metastatic renal cell cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2009 May 12. 26 p. (Evidence based series; no. 3-8-1). [39 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Inoperable locally advanced or metastatic renal cell carcinoma (RCC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Nephrology
Oncology
Pharmacology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether interferon-alfa (IFN-alfa) is an effective treatment option for patients with inoperable locally advanced or metastatic renal cell cancer (RCC)

TARGET POPULATION

Adult patients with inoperable locally advanced or metastatic renal cell carcinoma (RCC)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Interferon-alfa alone*
2. Interferon-alfa combined with other agents (not recommended outside of clinical trials)
3. Alternative treatments
    - Interferon-gamma
    - Medroxyprogesterone acetate

*__Note__: Interferon-alfa is not recommended as the preferred treatment option for inoperable locally advanced or metastatic renal cell carcinoma.Â Sunitinib and temsirolimus are preferred.

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Progression-free survival
- Tumour response rate
- Quality of life
- Toxic and adverse effects of drug treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE (1966 through May 2009) and EMBASE (1980 through 2009 week 19) were searched for relevant papers. MEDLINE was searched using the following medical subject headings: "carcinoma, renal cell", "kidney neoplasms", "immunotherapy", "interferon-alfa", and "interferon"; EMBASE was searched using the following Excerpta Medica tree terms: "kidney tumor", "kidney cancer", "immunotherapy", and "interferon." In each database, those subject headings were combined with the following disease and treatment-specific text words: "renal cancer", "kidney cancer", "immunotherap:", "interferon", and "IFN." Those terms were then combined with search terms for the following publication types and study designs: randomized controlled trials, controlled clinical trials, meta-analyses, systematic reviews, and practice guidelines.

In addition, the Cochrane Library databases (2009, Issue 2) and the meeting proceedings of the American Society of Clinical Oncology (ASCO) 1995-2008, the ASCO genitourinary symposia (2008-2009), and the American Urological Association (1995-2009) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (NGC)Â (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by four reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

Report Types

- Fully published randomized controlled trials (RCTs), abstracts of RCTs, or meta-analyses that compared interferon-alfa (IFN-alfa)-containing treatment regimens to regimens without IFN-alfa.

Study Types

- Randomized phase II and phase III studies.

Patient Characteristics

- Patients with inoperable locally advanced or metastatic renal cell carcinoma (RCC)
- RCTs including non-RCC patients were eligible as long as outcomes were analyzed separately for RCC patients.

Outcomes

- Reports were required to provide data on at least one of the following outcomes: response rate, survival (overall, progression-free, and time-to-progression), toxicity, and quality of life.

Controls

- Placebo
- Cytotoxic chemotherapy was considered a potentially appropriate control therapy on the basis of lack of anti-tumour activity and patient benefit identified in clinical trials.
- Hormonal therapies such as medroxyprogesterone (MPA) were considered appropriate control therapies on similar grounds to chemotherapy.
- Interferon-gamma (IFN-gamma) has been tested as a therapy for RCC but was considered as a control therapy equivalent to placebo for the purpose of this review. This assumption was considered justified by the results of a large RCT in RCC that reported no difference in objective response or survival when compared to placebo.

Exclusion Criteria

- RCTs that compared surgery or radiotherapy with IFN-alfa-containing treatment.
- RCTs that compared IFN-alfa with angiogenesis inhibitors were excluded as these comparisons are addressed in Evidence-based Series (EBS) #3-8-4.
- RCTs that compared IFN-alfa with interleukin-2 (IL-2) were excluded as these comparisons are addressed in EBS #3-8-2.

NUMBER OF SOURCE DOCUMENTS

Eight randomized controlled trials and 2 meta-analyses were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

For some eligible trials, odds ratios (OR) for overall mortality at one year and objective response, and hazard ratios (HR) for overall mortality were available

from a Cochrane meta-analysis. The analytic plan was to combine published data on these endpoints for all eligible trials, using meta-analysis. When the HR and its associated variance were available, those statistics were either extracted directly from the trial itself, from the Cochrane meta-analysis, or were obtained through personal communication with trial authors. Otherwise, the HR was estimated indirectly from data extracted from published Kaplan-Meier curves, using the methods of Parmar et al. If data were not provided from which HR could be derived, or the authors did not provide the HR, the trial was not included in the meta-analysis. To estimate the overall effect of interferon-alfa (IFN-alfa), the data were combined using Review Manager version 4.2. Results are expressed as HR or OR with 95% confidence intervals (CI), where values <1.0 represent a benefit for IFN-alfa over the alternative (for HR and OR of mortality), and values >1.0 indicate a benefit for IFN-alfa (for OR of response). Use of a random effects model was planned.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this evidence-based series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of the recommendations (Section 1 of the original guideline document) and the evidentiary base (Section 2 of the original guideline) of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Genitourinary Disease Site Group (GU DSG) circulated these guideline sections to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, four targeted peer reviewers from Ontario, Quebec, and British Columbia considered clinical and/or methodological experts on the topic were identified by the GU DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 25, 2009.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of genitourinary cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document), and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on March 15, 2009. The consultation period ended on April 15, 2009. The lead author reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Results from recent randomized trials indicate that inhibitors of angiogenesis such as sunitinib and temsirolimus are of superior clinical effectiveness to interferon-alfa (IFN-alfa) and therefore are recommended as preferred treatment options. (See the relatedÂ National Guideline Clearinghouse [NGC] guideline summary of Evidence-based Series [EBS] #3-8-4 Use of inhibitors of angiogenesis in patients with inoperable locally advanced or metastatic renal cell cancer).

- When angiogenesis inhibitors are not available or not recommended, single-agent IFN-alfa improves survival and disease control compared to older alternative therapies (such as IFN-gamma or medroxyprogesterone acetate) and represents a potentially effective alternative treatment option.
- The benefits of combined immunotherapy including IFN-alfa over IFN-alfa therapy alone are unclear, and this approach should not be routinely offered outside of clinical trials. (See the related NGC guideline summary of EBS #3-8-2 Interleukin-2 in the treatment of patients with unresectable or metastatic renal cell cancer).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Meta-analyses of randomized clinical trials (RCTs) comparing interferon-alfa (IFN-alfa)-based therapy with control treatment demonstrated an improvement in overall survival (six RCTs [n=992]; hazard ratio=0.79; 95% confidence interval, 0.69-0.91) with IFN-alfa-based therapy. This is equivalent to a 21% reduction in the risk of death over the time course of the RCTs included in this analysis.
- A Cochrane meta-analysis of four RCTs reported no difference with regards to efficacy between IFN-alfa2a and IFN-alfa2b.

POTENTIAL HARMS

In a large randomized controlled trial (RCT) comparing interferon-alfa (IFN-alfa) alone to medroxyprogesterone, lack of appetite, tiredness, nausea and vomiting, lack of energy, dry mouth, shivering, and depressed mood were more common with IFN-alfa therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The dose and duration of interferon-alfa (IFN-alfa) varied across trials. The largest trial reporting benefit gave one dose of 5 MU subcutaneously followed by 10 MU subcutaneously on a thrice weekly schedule for a total of 12 weeks until progressive disease discontinued or objective response continued longer.

- This guidance is issued as part of a series of articles on metastatic renal cell carcinoma (RCC) and as such does not address issues covered by the other guidelines.
- For patients with metastatic disease treated with cytoreductive nephrectomy, IFN-alfa should be prescribed in accordance with the doses used in the clinical trials. (See the related National Guideline Clearinghouse [NGC] guideline summary of Evidence-based Series [EBS] #3-8-3 The role of cytoreductive nephrectomy in metastatic renal cell cancer.)
- Both IFN-alf-2a and IFN-alfa-2b appear to have similar efficacy and toxicity.
- The effectiveness of IFN-alfa varies between patients. Its choice as therapy should be made in consultation with a physician experienced in the use of IFN-alfa, as the side effects of treatment can be substantial and must be considered with respect to the patient's age and performance status.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2009 May 12

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Genitourinary Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Genitourinary Disease Site Group (GU DSG) disclosed potential conflicts of interest relating to this systematic review. One author (SH) reported grant/research support from two companies with competing treatments, and serving on an advisory board for one company with a competing treatment. One author (CC) reported serving on an advisory board for two companies with competing treatments. No further conflicts were declared by the authors.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on December 30, 2009.

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